New-Onset Atrial Fibrillation
Sex Differences in Presentation, Treatment, and Outcome

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Background—Although sex differences in coronary artery disease have received considerable attention, few studies have dealt with sex differences in the most common sustained cardiac arrhythmia, atrial fibrillation (AF). Differences in presentation and clinical course may dictate different approaches to detection and management. We sought to examine sex-related differences in presentation, treatment, and outcome in patients presenting with new-onset AF.

Methods and Results—The Canadian Registry of Atrial Fibrillation (CARAF) enrolled subjects at the time of first ECG-confirmed diagnosis of AF. Participants were followed at 3 months, at 1 year, and annually thereafter. Treatment was at the discretion of the patients’ physicians and was not directed by CARAF investigators. Baseline and follow-up data collection included a detailed medical history, clinical, ECG, and echocardiographic measures, medication history, and therapeutic interventions. Three hundred thirty-nine women and 560 men were followed for 4.14±1.39 years.

Compared with men, women were older at the time of presentation, more likely to seek medical advice because of symptoms, and experienced significantly higher heart rates during AF. Compared with older men, older women were half as likely to receive warfarin and twice as likely to receive acetylsalicylic acid. Compared with men on warfarin, women on warfarin were 3.35 times more likely to experience a major bleed.

Conclusions—Anticoagulants are underused in older women with AF relative to older men with AF, despite comparable risk profiles. Women receiving warfarin have a significantly higher risk of major bleeding, suggesting the need for careful monitoring of anticoagulant intensity in women. (Circulation. 2001;103:2365-2370.)

Key Words: fibrillation ■ sex ■ anticoagulants

Analysis of Canadian Registry of Atrial Fibrillation (CARAF) data indicates that compared with men, women are older at the time of presentation, are more likely to seek medical advice because of symptoms, and experience significantly higher heart rates during atrial fibrillation (AF). Despite proven efficacy, warfarin remains underused in patients with AF, especially elderly women. However, women on warfarin appear to be particularly susceptible to major bleeds, suggesting the need for careful monitoring of anticoagulant intensity in this population.

Sex differences in coronary artery disease have received considerable attention,1–3 but few studies have dealt with sex differences in arrhythmias.4 AF is the most common sustained cardiac arrhythmia in the general population, and its incidence increases with age.5 Compared with women, men have a higher incidence of AF at all age groups.6 However, because there are almost twice as many women as men in the group with the highest percentage of AF, those aged ≥75 years, the absolute number of men and women with AF is equal.7,8

Little is known about sex differences in AF presentation, treatment, or outcome. Higher heart rates during AF have been reported in women compared with men,9 as well as more frequent recurrence of paroxysmal AF after successful cardioversion.10 Some studies have identified female sex as a risk factor for stroke in the presence of AF,11,12 but this has not been shown in all studies.13

Sex differences in presentation and clinical course may dictate different approaches to detection and management. Given the limited information available, we examined sex-related differences in AF by using data from CARAF. CARAF is a prospective observational study of subjects.
enrolled at the time of their first ECG-confirmed diagnosis of AF.

Methods

Patients
CARAF began enrollment of patients with newly diagnosed AF in 1990 in 6 cities across Canada (Vancouver, Calgary, London, Hamilton, Ottawa, and Montreal). A total of 1097 patients with ECG confirmation of AF have been enrolled in the study; 90% of the patients were enrolled before the end of 1994. Patients were recruited from physicians’ offices and emergency departments and during hospital admission for other diagnoses. Enrollees were obtained through routine, consistent screening of patients in emergency departments and of in-hospital patients and from consistent referrals from general practitioners.

CARAF Study Eligibility

Inclusion Criteria
Patients with a first diagnosis of AF or atrial flutter, confirmed by ECG, who presented because of symptoms or who were diagnosed during a routine physical examination were included in the study.

Exclusion Criteria
Patients were excluded for the following reasons: a previous history of AF; AF or flutter as a result of electrophysiology testing, angiography, or Swan Ganz or pacemaker insertion or removal; <1 year of expected survival because of a major life-threatening illness; inability to give informed consent; and inability to report for follow-up.

Data Collection
At the time of enrollment, a detailed baseline data form was completed that recorded symptoms (dizziness, fatigue, nausea, anxiety, chest pain, palpitations, dyspnea, presyncope, and syncope), clinical and laboratory data (thyroid and thyroid-stimulating hormone levels, blood pressure, and heart rate), medical history (cerebrovascular, cardiovascular, endocrine, smoking, and alcohol history), ECG and echocardiographic data (atrial and ventricular dimensions and valve status), medication history, and therapeutic interventions (pharmacological intervention and electrical cardioversion). Follow-up visits were conducted at 3 months, 1 year, and then annually. Detailed information regarding AF recurrence, medication usage, therapeutic interventions, and clinical history was collected at each follow-up visit. Treatment was at the discretion of each patient’s caregiver and was not directed by CARAF investigators.

Definitions
Recurrence of AF at each follow-up visit was classified into paroxysmal and chronic forms. Chronic AF was defined as suspected continuous AF, with ECG evidence, at 2 separate visits >7 days apart. Paroxysmal AF was defined as episodes of AF lasting <7 days that subsequently reverted to sinus rhythm. Reversion to normal sinus rhythm was predominantly induced (93%).

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics</th>
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<tr>
<td>Variable</td>
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<tr>
<td>Age at presentation, y</td>
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<tr>
<td>Heart rate during AF, bpm</td>
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<tr>
<td>Asymptomatic AF, %</td>
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<tr>
<td>History of bypass surgery, %</td>
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<tr>
<td>History of myocardial infarction, %</td>
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<tr>
<td>History of ischemic stroke, %</td>
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<td>Angina, %</td>
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<tr>
<td>Valvular heart disease, %</td>
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<tr>
<td>History of congestive heart disease, %</td>
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<tr>
<td>Peripheral vascular disease, %</td>
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<td>Hypertension, %</td>
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<td>Diabetes, %</td>
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<tr>
<td>History of hyperthyroidism, %</td>
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<tr>
<td>History of hyperthyroidism, %</td>
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<tr>
<td>Left ventricular hypertrophy by echocardiogram, %</td>
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<td>Fractional shortening, %</td>
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Values are mean±SE or percentages.

A major bleed was defined as one that required transfusion or surgical intervention or that resulted in a >20-g/L decrease in hemoglobin.

To facilitate analyses of medication usage, the following categories were defined: β-blockers, because these were the most frequently used medications for rate control, and the antiarrhythmic drugs sotalol, propafenone, and amiodarone, because these were the most frequently used antiarrhythmics.

Outcome events included progression to chronic AF, recurrence of paroxysmal AF, myocardial infarction, stroke, major bleed, and death. Treatment and recurrence of AF analyses were limited to 3 years of follow-up.

Statistical Analysis
Means of continuous variables were examined by the Student t test, and categorical variables were examined by the χ² test; for small sample sizes, the Fisher exact test was used. Risk of bleed was analyzed by using the Cox proportional hazards method. All significance tests were 2-sided, and a value of P<0.05 was chosen as the cutoff for statistical significance.

Results

Study Population
Of the 1097 subjects enrolled at baseline, 198 were excluded because their AF was precipitated by cardiothoracic surgery. This subgroup will be analyzed in a separate study. Of the remaining 899 subjects, 9 (1%) were lost to follow-up. Three-year visits were completed in 773 (86%) of the subjects.

Baseline Characteristics
Women constituted 38% (n=339) of the study cohort. Several differences in presentation and baseline medical history were
noted between men and women. Women were, on average, 5 years older (65.4±0.7 [women] versus 60.5±0.6 [men] years, P<0.001), more likely to seek medical advice because of symptoms (85.2% [women] versus 73.8% [men], P<0.001), and experienced higher heart rates during AF (126.2±1.9 [women] versus 119.1±1.4 [men] bpm, P=0.003) (Table 1). Heart rates during AF were determined from ECG recordings. The burden of ischemic disease was higher in men, but the prevalence of hypertension and history of thyroid dysfunction were significantly greater in women.

**Treatment**

Use of cardiac medications did not vary by sex. Medication usage at the time of diagnosis and again after baseline assessment and intervention is presented in Table 2. Digoxin was the most commonly prescribed medication for initial management in this cohort. Warfarin use at time of diagnosis was extremely low (2.8%) but increased over 10-fold by the conclusion of the baseline visit (31.6%).

Although the overall prevalence of antithrombotic use did not vary by sex (63.8%), the choice of therapy did. Women aged ≥75 years (n=67) were 54% less likely to receive warfarin but twice as likely to receive acetylsalicylic acid than were men aged ≥75 years (n=81). We modeled age and sex as predictors of antithrombotic use and demonstrated a significant interaction between sex and age ≥75 years (P=0.025).

To determine whether the lower usage in older women was due to a lower perceived risk of stroke, we examined warfarin use in the cohort aged ≥75 years with ≥1 stroke risk factor. Stroke risk factors included history of stroke or transient ischemic attack, hypertension, diabetes, or congestive heart failure. Among the elderly with ≥1 stroke risk factor, men (44.9%) were significantly more likely to be on warfarin than were women (24.5%) (P=0.034).

At the baseline visit, 69.9% of the cohort underwent acute pharmacological or electrical interventions to restore normal sinus rhythm, 52.8% underwent pharmacological therapy only, 15.2% underwent both pharmacological therapy and electrical cardioversion, and 2% underwent electrical cardioversion only. Men (19.6%) were more likely to undergo electrical cardioversion than were women (13.3%) (P=0.039). Conversion to normal sinus rhythm was equally successful in women (75.9%) and men (79.3%).

Over 3 years of follow-up, subsequent rates of therapeutic interventions (electric cardioversion 17.1%, radiofrequency ablation 2.7%, and pacemaker implantation 8.6%) did not vary by sex.

**Outcomes**

Recurrence of paroxysmal AF, determined either by ECG (documented) or by history of symptoms consistent with episodes of AF (undocumented), was recorded at each follow-up visit. The proportion of women with recurrences of AF (documented and undocumented) at each follow-up visit was significantly greater than the proportion of men with such recurrences (Figure 1).
TABLE 3. Major Bleeds in Subjects on Warfarin

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<tr>
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<th>n</th>
<th>Major Bleeds</th>
<th>RR*</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Women</td>
<td>10</td>
<td>9.2%</td>
<td>5.49</td>
<td>1.41–21.29</td>
</tr>
<tr>
<td>Men</td>
<td>5</td>
<td>2.8%</td>
<td>0.32</td>
<td>0.07–1.46</td>
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</table>

Percentages are proportion of subjects on warfarin who experienced major bleed during first 3 years of follow-up. Relative risk (RR) is relative to same sex not on warfarin.

*Age-adjusted RR of major bleed.

Despite the greater burden of paroxysmal AF, cumulative progression to chronic AF by the 3-year visit was identical in men and women (18.9%), and the mean time to progression was similar in women (1092 days) and men (1138 days) (P=0.35).

Total strokes (n=63), myocardial infarctions (n=32), and major bleeds (n=36) did not vary by sex (Figure 2). However, there was a significant interaction between sex and warfarin use for the risk of a major bleed (P=0.006). Women on warfarin were 3.35 times more likely to experience a major bleed than were men on warfarin. Nine of the 10 women who experienced a major bleed were aged <75 years.

CARAF did not collect international normalized ratio (INR) data at study visits; these data were reported only if the patient experienced a bleed. The mean INR for the 10 women on warfarin who had a bleed was 4.02±2.96, whereas INR in the men was 4.37±3.64 (P=0.787). The age-adjusted relative risk for a major bleed in women on warfarin compared with women not on warfarin was 5.49. Warfarin use was not a predictor of age-adjusted risk for a major bleed in men (Table 3).

There were 149 deaths in this cohort; 57.7% were due to cardiovascular causes. The major cardiovascular cause of death was arrhythmia (45%). Although women were as likely to die of cardiovascular causes as men, there were sex differences with respect to the types of cardiovascular death (Figure 3). Of the men who died, 17.5% died from congestive heart failure, compared with 5.8% of the women (P=0.045). The incidence of myocardial infarction did not vary by sex, but of the 5 fatal myocardial infarctions, 4 were in women (7.7%) (Fisher exact test, P=0.05). Adjustment for age did not alter the association. The “other” category included complications arising from peripheral vascular disease and perioperative death after cardiac surgery.

Discussion
In a cohort of adults with new-onset AF, women aged ≥75 years were half as likely to receive warfarin than were older men. However, women on warfarin, predominantly those aged <75 years, were 3.35 times more likely to experience a major bleed than were men on warfarin. Women were also significantly more likely to report undocumented episodes of paroxysmal AF at follow-up visits than were men, but the incidence of ECG-documented AF did not vary significantly by sex, nor did progression to chronic AF.

The finding that women are older at the time of first presentation with AF is consistent with the incidence of ischemic heart disease, a condition for which women are, on average, 10 years older than men at the time of presentation. The observation that women had faster heart rates during AF is consistent with the results of the Controlled Randomized Atrial Fibrillation Trial (CRAFT) studies in patients with symptomatic paroxysmal AF requiring drug therapy. One might speculate that given the older age of the women in this cohort, the increased heart rate might be due to lower vagal tone. However, adjustment for age did not alter the association. The greater prevalence of thyroid dysfunction in this cohort mirrors the female predominance of this disorder in the general population. The greater burden of ischemic disease among men may be a reflection of the relatively young age distribution of this population, in which the earlier manifestation of ischemic disease in men will contribute to a relatively greater burden. In an older cohort, this difference may not persist. The lower incidence of asymptomatic presentation at baseline among women is an interesting, though not unexpected, finding. In health surveys and studies of physical symptom reporting, women reported symptoms more frequently than did men.

Most of the trials demonstrating the benefit of warfarin for stroke prophylaxis in patients with AF were published in the early 1990s, around the time that CARAF recruited its first patients. Baseline visits for the CARAF cohort occurred between April 1990 and early 1996, with >90% completed before the end of 1994. This may explain the low usage of warfarin in this cohort. Although a delay in adopting evidence-based findings may explain the low overall use of warfarin, it does not explain why elderly women are less likely to receive warfarin than are elderly men. Recently published Stroke Prevention in Atrial Fibrillation III (SPAF-III) data specifically identify women aged >75 years as a high-risk group. The sex difference also does not appear to be related to differences in stroke risk. In the subgroup of subjects aged ≥75 years with ≥1 stroke risk factor, anticoagulant use was still significantly lower in women. Our results are consistent with those reported in a recent study that examined anticoagulant use in a community-based cohort in Northumberland, UK. In that study, anticoagulants were also found to be underused in elderly women. Our results are in contrast to the findings of Perez et al, who reported significant underuse of warfarin among patients aged ≥75 years (8.1%) compared with younger patients (42.2%), regardless of sex. In CARAF, warfarin usage, although low, did not significantly differ between those aged ≥75 years (29.1%) and those aged <75 years (32.4%).

Use of cardiac medications for the initial management of AF did not differ between the sexes. Digoxin was the most commonly prescribed medication at the baseline visit, after...
acute intervention to control ventricular rate. Antiarrhythmic agents were the second most commonly prescribed medications: sotalol (21.7%), propafenone (8.3%), and amiodarone (2.1%).

The greater incidence of recurrence of paroxysmal AF in women was due to a greater proportion of reported, but undocumented, AF. Although there was a trend to higher incidence of ECG-documented episodes of paroxysmal AF in women, this was not significant. Progression to chronic AF was also independent of sex. The greater incidence of reported, but not documented, AF may be a reflection of a female tendency to report symptoms more frequently than men. What is not clear is whether the undocumented episodes are truly AF or whether women are just more likely to feel any rhythmic disturbance. More frequent recurrence of paroxysmal AF in women was also reported by Sutterp et al., who used a definition of paroxysmal AF that is equivalent to our aggregate of ECG-documented and undocumented AF.

The overall incidence of stroke, myocardial infarction, and major bleed did not vary by sex, but women on warfarin were 3.35 times more likely to experience a major bleed, with 9 of 10 bleeds occurring in women aged <75 years. As expected, INRs at the time of bleeding were elevated, but the levels were similar in men and women. This finding has not been previously reported in any of the major AF trials. The results of the present study may be a reflection of the difference in the intensity of monitoring in a clinical trial setting versus real-life practice. It is interesting to note that a recent study of oral anticoagulant use and risk of bleeding in a population after hospitalization for deep-vein thrombosis also reported an increased risk of bleeding associated with female sex (relative hazard 1.7, 95% CI 1.3 to 2.2). Clinical trials of thrombolytic regimens have also shown an increased risk of the bleeding among women.

CARAF is subject to many of the limitations inherent in observational studies. Selection and referral biases are 2 important considerations in the present study. The majority of patients were recruited from emergency departments (41%) or hospital admissions for other diagnoses (30%), which were predominantly cardiovascular in origin. Although potentially limiting the generalizability of our findings, CARAF nevertheless provides insights into current patterns of practice in this population. Women (64.9%) were as likely to be recruited from hospital admissions or emergency departments as were men (64.9%). Selection and referral biases, if present, appear to be independent of sex, which is the focus of the comparisons in the present study.

Misclassification of baseline comorbidities and recurrence of AF is also possible. We relied on patient interviewers, by trained nurses, to obtain medical history. Thus, the accuracy of comorbidity information is largely dependent on patient recall, although the presence of some comorbidities (such as hypertension and diabetes) could be corroborated by medication usage. Nevertheless, misclassification is likely to be nondifferential with respect to sex. Recurrence of AF was monitored at annual visits and thus was subject to patient recall regarding events in the previous year. Research suggests that women are more likely to report symptoms than are men, and this may explain the higher incidence of undocu-

References
